REMARKS

By a non-final Office Action dated October 2, 2006, the Examiner in charge of this case rejected the claims of this application on a variety of grounds. Claims 1-28 are currently pending in the application; Claims 16-18 and 25-27 are withdrawn from consideration as drawn to a non-elected invention; Claims 1-5, 7-15, and 28 are rejected under 35 U.S.C. 112, 2nd paragraph; Claims 1-3, 7-10, 12-15, and 19-24 are rejected under 35 U.S.C. 103(a); and Claims 1-15, 19-24, 28 and 29 are rejected under obviousness-type double patenting.

Applicants thank Examiner Staples and Supervisor Horlick for conducting a telephonic interview on December 21, 2006 with Dr. Robert Lowery and the applicants' undersigned representative to clarify the obviousness-related issues recited in the first Office Action. In response, applicants submit the amendments above, arguments set forth herein below, and the enclosed Declaration of Dr. Robert G. Lowery. Based on this submission, applicants respectfully request reconsideration and withdrawal of all the rejections set forth in the Office Action.

Election/Restrictions

The finality of the restriction requirement is acknowledged. However, applicants continue to traverse the Examiner requirement for restriction and reserve the right to file a divisional application drawn to the non-elected claims.

Information Disclosure Statement

Applicants submit that Information Disclosure Statements were filed in the present application on April 30, 2004; May 26, 2004; March 14, 2005; and May 16, 2005. These Statements are believed to be complete. Applicants recognize that only patents and publications cited in these Statements are considered by the Examiner.

Specification Amendments

At the suggestion of the Examiner, applicants amend the specification to capitalize the trademarks, BODIPY™ and ALEXA™ and to define these marks by their generic terminology.

Claim Amendments

At the outset, applicants wish to direct the Examiner's attention to the claim amendments submitted to the USPTO on September 5, 2006 in response to the Restriction Requirement. Specifically, it appears the amendments to independent Claim 1, elements (c) and (d) and Claim 19 may not have been fully appreciated or addressed in the current Office Action. Applicants believe these claim amendments obviate at least some of the rejections cited in this Action.

Furthermore, independent Claims 1, 19, 28 and 29 are amended to more clearly define the nature of the claimed embodiments as a "homogenous assay" utilizing an antibody to specifically detect the donor-product without removal or alteration of any residual donor molecule. The phrase "homogenous assay" is supported in the specification and is defined, for example, at pg. 2, ¶7. Claims 3 and 4 are believed redundant and are canceled without prejudice or disclaimer. Also, based on the issues discussed during the Examiner interview, Claims 1 and 19 are further amended to more clearly define the scope of the donor molecule, as comprising a nucleotide attached to a covalent adduct, X.

Support for these claim amendments is found for example, throughout the specification, specifically at pg. 1, ¶ 5, pg. 2, ¶7 to pg. 5, ¶16; pg. 6, ¶18; pg. 7, ¶¶ 19-21; pg. 9, ¶ 41; pg. 11, ¶50 to pg. 12, ¶ 61. No new matter is added by the introduction of these claims.

Claim Rejections 35 USC §112

Claims 1-5, 7-15, and 28 stand rejected under 35 USC 112, 2nd paragraph, as being indefinite for various reasons. Specifically, the terms "donor molecule" and "macromolecule" in Claims 1 and 28 are believed to be indefinite and clarification is requested.

In regards to the donor molecule, applicants wish to clarify a technical point. Unless a reaction runs to completion – which is rarely the case – there is always residual donor molecule remaining when the detection step occurs. For example, high throughput screening (HTS) assays and enzymatic assays, in general, are almost always run under initial velocity conditions. This means the reaction is terminated before substantial depletion of substrate(s), generally less than 30%, has occurred. This is done because, if too much substrate is consumed, the reaction rate decreases, resulting in a non-linear relationship between enzyme activity and assay output. Furthermore, the assumption of initial velocity conditions defines

the selectivity of the claimed detection method; i.e., the ability to detect donor-product, suitably ADP, in the presence of excess donor molecule, suitably ATP, as described in the application.

Other assay methods require (1) the residual donor molecule be removed from the reaction or (2) the donor-product be converted to something else for detection to occur. However, applicants' are the first to make a competitive immunoassay that is capable of direct, homogenous detection of donor-product in the presence of donor molecule. No other immunoassays –or even antibodies- recognize donor-product with high selectivity over donor molecule. Thus, for reasons of clarity and not patentability, applicants incorporated the initial velocity assumption into the claims. As indicated above, amended Claim 1 affirmatively refers to a "homogenous assay" in the preamble. Also, amended Claim 1 includes the phrase "partially consuming the donor molecule" in step (b).

Next, the Examiner indicates that clarification is required relating to the competitive displacement of a detectable tag by donor product. In response, Claim 1 was amended to clarify the macromolecule is an antibody. With this amendment, there should be no confusion about how a donor product displaces a detectable tag; i.e., the operating principle of a competitive immunoassay. Binding of antigen to an antibody should not require further explanation to one of ordinary skill in the art. Also, it would be generally understood that since the unmodified donor-product acts by "competitively displacing" the detectable tag, the two molecules are binding to the same site on the antibody.

Claim 23 is also amended to recognize that ALEXA FLUOR® is a trademark.

Claim Rejections 35 USC §103

Claims 1-3, 7-10, 12-15, and 19-24 stand rejected under 35 U.S.C. 103(a) as being obvious over Seethala in view of either Li et al. or Gassler et al. It appears the Examiner is arguing that because Seethala discloses the use of a competitive binding assay for phosphopeptides as a kinase detection method, and Li et al. and Gassler et al. disclose the use of binding assays for adenine nucleotides, the combination of these documents makes obvious the use of a competitive binding assay for ADP as a kinase assay method. Applicants respectfully disagree.

At the outset, applicants submit that the claimed methods relate to a broad universal, homogenous assay that uses a single set of detection reagents across an entire family of enzymes, as described throughout the specification. In contrast, the assays disclosed in the documents cited by the Examiner relate only to kinases. Regardless of the specific enzyme disclosed, the cited documents does not teach, suggest or motivate one skilled in the art to arrive at the claimed embodiments. There are numerous reasons for Seethala's inability to motivate others, either alone or combined with Li et al. or Gassler et al. For example, applicants submit that (1) at the time the invention was conceived, the detection of donor-product, such as ADP using a competitive binding assay was not equivalent to detection of phosphopeptides using a competitive binding assay; (2) neither Li et al. nor Gassler et al. disclose the use of a competitive binding assay for detection of a molecule produced in an enzyme reaction; and (3) neither Li et al. nor Gassler et al. involve an antibody as the macromolecule component of their binding assays. Each is discussed later below in more detail. Also, as further evidence of non-obviousness, applicants enclose herewith a Declaration by Dr. Robert G. Lowery, along with *Exhibit A (*his *curriculum vitae)*. Dr. Lowery's Declaration is intended to show the claimed process and products are commercially successful and this commercial success is directly attributable to the process and products defined by the claims.

In regard to Seethala, applicants submit that it discloses detection of the acceptor-X product of a group transfer reaction - a phosphopeptide in the case or kinases – <u>not</u> detection of the donor-product as claimed by applicants. This patentable distinction is clearly recognized by the Examiner and set forth at page 9, 1st para. of the Present Office Action:

> "Seethala does not teach the obverse method of detection. That is, Seethala does not teach where the tag is coupled to the donor product, ADP. Consequently, Seethala does not teach detection of the donor product, ADP, by its displacement of the tagged donor product, ADP."

However, it appears the Examiner considers detection of the acceptor-X and detection of the donor product to be equivalent. This is made explicit later at page 9, last para. of the Office Action, which provides:

> "Also, it was known to one of ordinary skill in the art that measurement of any product of a reaction could be used to monitor that reaction."

This is theoretically true for any reaction where two products are formed. However in a practical sense, if detection of the two products are not equivalent; i.e., if there are large differences in the relative difficulty of developing detection methods for the two products, then one skilled in the art would be less inclined to pursue – or to even consider – the more difficult approach. Detecting the acceptor-X – a phosphopeptide – using an immunoassay as in Seethala was common practice at the time of the invention; antibodies to phosphopeptides were commercially available and widely used. In contrast, a homogenous assay for direct detection of donor-product, e.g., ADP in the presence of ATP using an antibody was not known at the time of the invention. There was no commercial source of anti-ADP antibodies available, and as described below, their development presented significant technical barriers. Accordingly, using a homogenous immunodetection assay to directly detect ADP in the presence of ATP was not equivalent to using phosphopeptide detection from the perspective of someone of ordinary skill in the art.

In fact, there is evidence that Seethala's approach, which was originally published more than five years before our invention was conceived, became widespread (see, Seethala, R. and R. Menzel, A homogeneous, fluorescence polarization assay for src-family tyrosine kinases. *Anal Biochem*, (1997) 253(2): p. 210-8). At the time applicants claimed embodiments were conceived, at least three companies were selling kinase assay products based on Seethala's method. Yet, no one conceived of ADP immunodetection until applicants disclosed a method which makes immunodetection more useful than phosphopeptide detection. Further evidence the claimed subject matter solved a problem that was long standing in the art is set forth in Dr. Robert G. Lowery's Declaration (enclosed herewith). Thus, Seethala does not teach, suggest or motivate one of ordinary skill to make the claimed embodiments.

Next, the Examiner indicates that Li et al. disclose

> "...where a fluorescent tag is coupled to adenine, a nucleotide, and can compete with untagged adenine for a binding site on a macromolecule, with measurable change in fluorescence polarization of bound and unbound tagged adenine." (See page 9, para. 3 of the Office Action)

In response, applicants submit the detection method of Li et al. does not cure the deficiencies of Seethala. There is no untagged adenine present in Li et al. Therefore,

contrary to applicants invention, Li's method does not rely on untagged adenine for "competitively displacing" tagged adenine or a nucleotide. Instead, in Li's method, the tagged adenine is enzymatically transferred to a protein where it remains covalently bound, resulting in an increase in its polarization. To adapt the method of Li for detection of kinases, one would need to use fluorescently labeled ATP as a donor molecule. This is not what applicants claim and there is nothing in the literature suggesting that such an approach would work. The fluorescent label would need to be attached to the terminal phosphate of ATP, which would very likely affect its ability to serve as a substrate for many protein kinases.

Additionally, applicants amend Claim 1 herein to refer to an antibody. The macromolecule in Li et al is not an antibody. Thus, Li et al. disclose neither the use of a competitive binding assay for detection of ADP (nor any other nucleotide), nor the case wherein the competitive binding assay is a homogenous immunodetection assay. Likewise, Gassler et al. does not cure the deficiencies of Seethala or Li et al. Gassler et al. does not use a homogenous immunodetection assay as the competitive binding assay (see, page 10, para. 2 of the Office Action). In Gassler et al., the quenching of fluorescently labeled ADP was used to monitor its rate of displacement from a protein by an excess of unlabeled ADP. The method is not being used, nor is there any suggestion of its use, for detecting ADP produced in an enzyme reaction. In fact, in the same document, they use a radioactive assay to measure the ADP formed in the ATPase enzyme reactions they are studying. Also, the binding protein in Gassler et al. is not an antibody. Moreover, neither the Li nor Gassler methods enable the detection of ADP in the presence of excess ATP, which is a claimed element of applicants' invention.

The Examiner also suggests that Li et al. and Gassler et al. disclose the tagging of ADP with a fluor to produce a tracer for the assay described in applicants' invention (see page 10, para. 2 of the Office Action). However, although these documents disclose the concept of a fluorescently tagged nucleotide, they do not disclose the structural details required for a tracer to adequately perform applicants' methods. Elements such as the number of carbons in the linker region or the type of fluor have a significant impact on the parameter of the detection method: selectivity for ADP vs. ATP. Such elements would not be obvious to one of ordinary skill in the art. One would not intuit that the structure of the fluor attached to the adenine portion of the tracer would affect the selectivity of an antibody for the

ribose-phosphate moiety of unmodified ADP. Indeed, although this is an important element of the claimed methods, applicants' still do not understand how this occurs.

A related concept is that the tracers developed by applicants are unique from others described in the literature. Whereas the methods for tracer synthesis are generally known, the structures that proved successful for practicing the claimed methods were not known. In fact, applicants were forced to design distinct tracer structures for practicing embodiments of the invention, which are claimed in a continuation-in-part application, U.S. Application No. 11/137,947. This speaks to the difficulty of developing a competitive immunoassay for ADP, and the lack of any literature references that could be directly used for development of a tracer for the claimed assay method. Accordingly, Li et al. and Gassler et al. alone or in combination do not cure the various deficiencies of Seethala.

Claims 4, 6, 11, 28, and 29 stand rejected under 35 U.S.C. 103(a) as being obvious over Seethala in view of Seethala in view of either Li et al. or Gassler et al. as applied to claims 1-3, 7-10, 12-15, and 19-24 above, and further in view of Bredehorst. The arguments presented against Seethala in view of either Li et al. or Gassler continue to apply here. Specifically, the Examiner asserts that Bredehorst et al disclose how to develop an antibody against ADP that would enable its preferential detection over ATP (see page 10, last para. of the Office Action). Applicants respectfully disagree.

In response, applicants submit that in general Bredehorst teaches away from the development of antibodies to ADP. Specifically, Bredehorst teaches away from the development of antibodies with sufficient selectivity to allow detection of, for example, ADP in the context of a kinase reaction; i.e., in the presence of excess ATP. Bredehorst attempted to develop polyclonal antibodies against an ADP-ribose antigen. Bredehorst concluded that much of the injected ADP-ribose antigen (which had been conjugated to carrier protein) was hydrolyzed at the pyrophosphate linkage to form 5'-AMP, resulting in antibodies exclusively to AMP or to both 5'-AMP and ADP-ribose, depending on the antigen used. In characterizing these antibodies, Bredehorst found that one of the polyclonals generated bound weakly to ADP (less than 1/50th the affinity for AMP) and an additional 16-fold more weakly to ATP. This result was cited as providing an approach to develop an antibody for quantifying ADP over ATP.

However, the selectivity for ADP vs. ATP required for the method was thought to be 500- to 1,000-fold at the time method was conceived, so the 16-fold selectivity observed by Bredehorst et al was woefully inadequate. If Bredehorst found the rabbit immune system was capable of differentiating between ADP and ATP with only 16-fold selectivity, how would that motivate one of ordinary skill in the art to attempt to attain selectivity of 500- to 1000-fold? On the contrary, Bredehorst's results taught that production of antibodies suitable for the claimed method would be highly unlikely.

Moreover, Bredehorst used an ADP-ribose antigen and the observed cross-reaction with ADP was fortuitous. Presumably, if one were intending to develop antibodies with high selectivity for ADP, ADP would be used as an antigen, not ADP-ribose. However, based on Bredehorst, one would conclude that attempting to develop an antibody to an ADP antigen would result in hydrolysis at the pyrophosphate bond to form AMP, yielding – at best - a mixed population of antibodies against ADP and AMP with little selectivity with respect to ATP. Thus, in this regard too, Bredehorst teaches away from the development of antibodies against ADP. Additionally, one with skill in the art who was investigating this approach would likely have concluded that ADP would be even more labile than ADP-ribose in the serum of a rabbit or mouse because of the presence on the surface of platelets of nucleotidases that dephosphorylate ATP and ADP (see Koszalka, P., et al., *Targeted disruption of cd73/ecto-5'-nucleotidase alters thromboregulation and augments vascular inflammatory response. Circ Res,* (2004) 95(8): p. 814-21; and Nishio, H., et al., *Effect of concanavalin A on 5'-nucleotidase activity of rabbit blood platelets. Jpn J Pharmacol,* (1987) 43(2): p. 230-3.)

Accordingly, applicants submit that absent such a showing to combine the cited documents, the Examiner has impermissibly used "hindsight" to reject the claims. It appears the Examiner inadvertently used applicants' teaching as a blueprint to look through the cited art and piece together (somewhat out of context) elements therein to defeat the patentability of the claimed embodiments. This type of examination is unreasonable and prohibited by the MPEP 2142. Thus, neither the combination of Seethala, Li et al., Gassler et al., and Bredehorst et al. nor any other evidence of record, establish a *prima facie* case of obviousness for the claimed embodiments.

Next, Claims 4, 5, 6, 11, 28, and 29 stand rejected under 35 U.S.C. 103(a) as being obvious over Seethala in view of either Li et al. or Gassler et al. as applied to claims 1-3, 7-10, 12-15, and 19-24 above, and further in view of Kawamitsu. Applicants respectfully disagree.

Again, the arguments presented against Seethala in view of either Li et al., or Gassler continue to apply here. In regard to Kawamitsu et al., it disclosed that monoclonal antibodies generated from poly-ADP-ribose polymers can cross react with Ado(P)-Rib-P, the monomer unit of poly-ADP-ribose. This document does not disclose how to develop antibodies that selectively recognize ADP in the presence of ATP. No monoclonal antibody developed by Kawamitsu shows selectivity for one mononucleotide vs. another mononucleotide. Also, there is no rationale for applying their approach of using a polynucleotide antigen for development of such an antibody. Thus, Li et al., Gassler et al., and Kawamitsu, alone or in combination do not cure the various deficiencies of Seethala.

Double Patenting

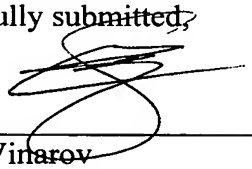
Next, Claims 1-15, 19-24, 28 and 29 stand rejected under a provisional obviousness-type double patenting as being unpatentable over Claims 8-16 and 18 of co-pending U.S. Application No. 11/353,500 by Lowery et al.

Applicants acknowledge the provisional rejection and the suggestion of filing a terminal disclaimer. However, applicants submit that U.S. Application No. 11/353,500 has not yet issued as a patent and a terminal disclaimer is premature at this stage. Furthermore, based on the amendments and the arguments made hereinabove, applicants believe that a provisional double patenting rejection is unwarranted.

Accordingly, applicants respectfully request that in view of these claim amendments and remarks, the rejection be respectfully reconsidered, withdrawn and that a timely Notice of Allowance be issued in this case.

No fees are believed to be due. If any fee is due or any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the fees to Deposit Account No. 17-0055.

Respectfully submitted,



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